PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 07 July 2005 (07-07-2005)

Applicant's or agent's file reference
93764-1

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2005/000345	04 March 2005 (04-03-2005)	04 March 2004 (04-03-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 35/12; C12N 5/02; C12N 5/10; C12N 15/86

Applicant
MEAKIN, SUSAN, ORIOLE et al

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
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Authorized officer

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] This opinion has been established on the basis of a translation from the original language into the following language ,which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      [X] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [X] in written format

      [X] in computer readable form

   c. time of filing/furnishing

      [X] contained in the international application as filed.

      [X] filed together with the international application in computer readable form.

      [ ] furnished subsequently to this Authority for the purposes of search.

3 [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claim Nos. 1 to 19

because:

[X] the said international application, or the said claim Nos. 1 to 19
relate to the following subject matter which does not require an international preliminary examination *(specify)* :

Although claims 1 to 19 encompass a method of treatment of the human/animal body which this Authority is not required to examine under Rule 67.1 (iv) of the PCT, the written opinion has been established on the basis of the alleged effects of FRS3 referred to therein.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claim Nos.
are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed.

[ ] no international search report has been established for said claims Nos.

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form [ ] has not been furnished

[ ] does not comply with the standard

the computer readable form [ ] has not been furnished

[ ] does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 1-3	YES
	Claims 4-26	NO
Inventive step (IS)	Claims 1-3	YES
	Claims 4-26	NO
Industrial applicability (IA)	Claims 1-26	YES
	Claims None	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: MCDOUGALL, K. et al. MECH DEV. May 2001, Vol. 103, No. 1-2, pages 145-148
D2: ZHOU, L. et al. MOL BIOL REP. March 2003, Vol. 30, No. 1, pages 15-25
D3: OSTENFELD T. et al. Recent Advances in Stem Cell Neurobiology. ADV TECH STAND NEUROSURG. 2003, Vol. 28, pages 3-89

Novelty and Inventive Step - Articles 33(2) and 33(3) PCT

The problem to be solved by the instant application is the identification of a method to achieve increased precursor cell proliferation in culture in order to obtain greater numbers of the cells which can subsequently be used in differentiation methods and/or cell therapy protocols. Specifically, the instant application discloses that transgenic precursor cells, namely, skin-derived precursors and neural crest stem cells, engineered to overexpress FRS3, proliferate to a greater extent in culture and thus, yield a greater number of cells.

Document D1 discloses the expression pattern of FRS3 in developing tissues during murine embryogenesis. FRS3 expression was detected in fetal brain, heart, liver, and stomach with predominant expression in the ventricular layer of the developing neural tube. In adult tissue, FRS3 expression was detected in kidney, spleen, brain, lung, large intestine, testis, stomach, liver, bone marrow, and small intestine.

Document D2 discloses the genomic organization of the mouse and human FRS3 genes. As a first step, document D2 discloses the use of primers derived from murine FRS3 cDNA to isolate overlapping fragments of genomic FRS3 DNA from 129/SVJ murine embryonic stem cells (i.e. precursor cells comprising a nucleic acid molecule encoding FRS3). In addition, document D2 discloses FRS3 expression in the developing embryo and neural tube during neurogenesis.

Document D3 discloses neural precursor cells as well as pharmaceutical compositions comprising said cells which are useful in the treatment of nervous system defects which may be "characterized by the premature death or malfunction of a specific cell type", following transplantation. Further, document D3 discloses the option of genetically modifying the precursor cells to express therapeutically active peptides as well as the directed differentiation of precursor cells and thus, induction of specific cell types.

continued: see supplemental sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The description does not meet the requirements of Article 5 PCT because it does not contain sufficient technical information required to enable a skilled person to put all embodiments of the claimed method into practice. In particular, claims 1 to 3, 10, 11, and 14 to 19 merely refer to "modulating the expression of FRS3". However, according to page 12, paragraph [0047], of the description the term "modulation" includes chemical means by "exposure to a chemical or compound that increases expression of the FRS3". However, the description does not disclose or identify any compound(s) which may be defined beyond an insufficient statement of the desired result to be achieved. In fact, a skilled person would be required to exercise undue experimentation in order to identify compound(s) which would be capable of the alleged effects.

Claims 1 to 3, 10, 11, and 14 to 19 do not meet the requirements of Article 6 PCT. These claims lack clarity as they are merely defined as a result to be achieved. In particular, the method step defined as "modulating the expression of FRS3" lacks clarity. The claims must include a step or series of steps which specify how "modulating" is accomplished in order to achieved the desired result, namely, precursor cell proliferation. In addition, these claims do not specify that all method steps occur *in vitro* and are thus interpreted to encompass a method of treatment of the human/animal body. Furthermore, in view of the description, an essential feature of the invention is missing, namely, enhanced proliferation is achieved when expression of FRS3 is increased in comparison to native FRS3 levels, via transgene overexpression of FRS3 under the second intronic region enhancer of the nestin gene and minimal TK promoter.

Claims 10 and 11 do not meet the requirements of Article 6 PCT because they lack clarity. Specifically, there is no antecedent basis for "modulating" in all listed dependent claims, for instance, claim 6.

Claims 18 and 23 do not meet the requirements of Article 6 PCT. Inclusion of the term "substantially" causes a lack of clarity.

Claims 20 to 26 do not meet the requirements of Article 6 PCT. The claimed precursor cell, progeny cell, and pharmaceutical composition comprising said cells are not adequately defined. In particular, these claims lack clarity because they encompass any or all cell types and are merely defined as comprising a nucleic acid molecule encoding FRS3. Thus, these claims fail to recite any distinguishing technical features of the claimed products over natural counterparts whose genome comprises a nucleic acid molecule encoding FRS3. Moreover, in view of the description, an essential feature of the invention is missing, namely, that the precursor cell contains an FRS3 transgene whereby overexpression is driven by the second intronic region enhancer of the nestin gene and minimal TK promoter. Consequently, the subject matter and scope of protection sought requires clarification.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V: 2. Citations and Explanations

It is known independently from documents D1 and D2 that FRS3 is expressed in developing tissues and precursor cells, for instance, embryonic stem cells. However, the role of FRS3 in precursor cell proliferation has not been disclosed in the cited prior art. In addition, both document D1 and D2 acknowledge that the role of FRS3 has not been elucidated. Therefore, the prior art would not have guided a skilled person to the conclusion that modulation of FRS3 expression in precursor cells would enhance precursor cell proliferation. Thus, novelty and inventive step are acknowledged for claims 1 to 3 which comply with Articles 33(2) and 33(3) PCT.

In general, it can be said that claims 3 to 19 set forth the use of precursor cells in a cell therapy protocol. However, the use of precursor cells, as well as differentiated cells derived therefrom, in cell therapy protocols is well documented in the prior art, for example, as disclosed in document D3. Further, claims 4 to 19 merely specify that the precursor cell "has been proliferated by modulating the expression of FRS3" or that the precursor cell comprises genomic FRS3. However, these features do not specify any unique or distinguishing technical characteristics of precursor cells over precursor cells obtained and used by prior art methods, for instance, as disclosed in document D3. Notably, a new method of manufacture, in this case a new culture method, does not reinstate novelty to an old and known cell type and/or old and known uses thereof. Consequently, claims 4 to 19 do not meet the criteria of novelty and inventive step under Articles 33(2) and 33(3) PCT.

Likewise, claims 20 to 26 are directed to a precursor cell, progeny cell, or pharmaceutical composition comprising said cell which, are broadly defined as comprising a nucleic acid molecule encoding FRS3. As noted above, it is known independently from documents D1 and D2 that FRS3 is expressed in developing tissues and precursor cells, for instance, embryonic stem cells. It follows that the claims do not define a novel cell type because the presence of genomic FRS3 is an inherent property of the claimed cells. Likewise, the claims encompass the precursor cells and pharmaceutical compositions disclosed in document D3. Consequently, claims 20 to 26 do not meet the criteria of novelty and inventive step under Articles 33(2) and 33(3) PCT.

Industrial Applicability - Article 33(4) PCT

Claims 20 to 26 appear to define subject matter that has industrial applicability under Article 33(4) of the PCT, based on the enhancement of precursor cell proliferation as a result of FRS3 transgene overexpression.

For the assessment of claims 1 to 19 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT. Further, the patentability of said claims can depend upon their formulation. Although the methods *per se* defined in claims 1 to 19 relate to subject matter which this Authority is not obliged to examine under Rule 67.1 (iv) of the PCT, the use of FRS3 overexpression referred to therein to enhance precursor cell proliferation appears to represent subject matter that has industrial applicability.